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Metastatic anorectal melanomas – An exploratory retrospective analysis on the benefits of systemic therapy versus best supportive care in a resource-limited setting from India

Arvind Sahu, Anant Ramaswamy, Nitin Singhal[1], Vipul Doshi, Jimmy Mirani, Ashwin Desouza[1], Shripad Banavali, Avanish Saklani[1], Vikas Ostwal

Abstract

Aim: Data regarding the optimal management of metastatic anorectal melanoma (mARM) is scarce. The primary aim was to evaluate the potential benefits of systemic therapy in mARM. **Materials and Methods:** This is a retrospective analysis of all mARM who presented between July 2013 and June 2015 at the Department of GI Medical Oncology, Tata Memorial Hospital. **Results:** Of a total of 37 patients, twelve patients were planned for best supportive care (BSC) only while the remaining 25 patients received systemic therapy. The median overall survival (OS) for the whole cohort was 27 weeks. The OS was significantly better in patients who received first-line therapy as compared to those who were offered BSC (median OS: 14 vs. 33 weeks; $P = 0.04$). Patients with PS of 1 did significantly better than PS of 2 more (OS 70 vs. 17 weeks; $P = 0.015$). **Conclusion:** mARM should be offered chemotherapy, especially in good performance patients. Paclitaxel/Platinum or Capecitabine/Temozolomide regimens can be considered as the preferred regime in the resource-limited setting where immunotherapy may not be a feasible option.

Key words: Anorectal melanoma, chemotherapy, metastatic, overall survival

Introduction

Mucosal melanomas arise from the mucosal epithelium lining the respiratory, alimentary, and genitourinary tracts, all of which contain melanocytes. They account for approximately 1% of all melanomas, with the most common sites of origin being the head and neck, anorectal, and vulvovaginal regions (55%, 24%, and 18% of cases, respectively). Rarer sites of origin include the urinary tract, gall bladder, and small intestine.[1,2] Mucosal melanomas portend a worse prognosis than those arising from cutaneous sites.[2] Owing to the rarity of this entity, its heterogeneous presentation in terms of location and its unique biology,[3] management strategies are based on individual experience and small case series available from literature.

Anorectal mucosal melanoma accounts for approximately 0.05% of all colorectal malignancies and 1% of all anal canal cancers.[4] Patients without distant metastases but nodal metastasis at presentation have poor prognosis with a median OS of 8 months.[5] Data regarding the optimal management of metastatic anorectal melanoma is scarce. These patients are usually offered supportive or palliative care at most of the centers.[6] There are no prospective studies assessing the optimal approach to the treatment of metastatic anorectal melanoma due to the small numbers of this patient population. Various chemotherapeutic regimens used include temezolomide, DTIC, Taxanes, and Thalidomide among others.[3,7-14] As of date, there is no evidence to suggest the benefit of any form of systemic therapy over the best supportive care (BSC) alone.[8]

With innovative-targeted therapy and immunotherapy, patients can survive for many years. Unfortunately, new therapies are expensive. According to a survey conducted by Dr Lidija Kandolf-Sekulovic, over 5000 patients with metastatic melanoma in Europe have no access to these drugs.[15,16] Ipilimumab (Yervoy; Bristol-Myers Squibb, New York, NY) approved by the Food and Drug Administration for the treatment of metastatic melanoma had a survival benefit over and above standard treatment arms of 3.7 months in previously treated patients and 2.1 months in previously untreated patients but at a staggering cost of $120,000 for 4 doses. The drug is hardly alone in the race for lofty pricing of innovative melanoma drugs.[17]

Our total health-care expenditure stands at 4.1 per cent of GDP, and the private health-care sector is responsible for the majority of healthcare in India. Most health-care expenses are paid out of pocket by patients and their families, rather than through insurance. This has led many households to incur Catastrophic Health Expenditure (CHE) which can be defined as health expenditure that threatens a household's capacity to maintain a basic standard of living.[18] One study found that over 35% of poor Indian households incur CHE. The poorer patients are usually left with fewer options of health-care services access.[18]

The purpose of this study was to evaluate the demographic profile, presentation, and outcomes of 37 patients diagnosed with metastatic anorectal melanoma and treated at our institution during the period of 2013–2015. The primary objective was to evaluate the potential benefits of offering systemic therapy to such patients who have preserved performance status (PS).

Materials and Methods

This study is a retrospective analysis of a prospectively maintained database of all metastatic anorectal melanoma patients who presented between July 2013 and June 2015 at the Department of GI and Hepato-pancreato-biliary Oncology, Tata Memorial Hospital, Mumbai. Demographic clinical and radiological data were obtained from patient records including electronic medical records. Patients who presented to us in the

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Departments of Medical Oncology and [1]Surgical Oncology, TMH, Mumbai, Maharashtra, India
Correspondence to: Dr. Vikas Ostwal,
E-mail: dr.vikas.ostwal@gmail.com

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above study period were divided into the following categories based on the treatment modality received (as per physician discretion as immunotherapy was still unavailable due to logistic and financial issues):

1. BSC
2. Chemotherapy ± oral metronomic therapy (OMCT).

OMCT used in these patients with metastatic melanoma is an in-house investigational protocol developed for patients with progressive disease in varied solid tumors and comprises tamoxifen, propranolol or thalidomide, sodium valproate, metformin and/or celecoxib. OMCT was combined with chemotherapy in some patients as per physician's choice. Patients were followed up every 3 months for the evaluation of response to treatment. Response of treatment was recorded as per RECIST criteria and evaluated with computed tomography (CT) scans every 2–3 months interval. Response was categorized into four categories as complete response, partial response (PR), stable disease (SD), and progression disease (PD).[19]

Clinical data collection and statistics

All data were recorded and analyzed using IBM SPSS Statistics ver. 20 (IBM Co., Armonk, NY, USA). Survival outcomes in terms of progression-free survival (PFS) and overall survival (OS) were analyzed. Progression-free survival was calculated from the date of diagnosis of metastatic disease to the date of clinical or radiological evidence of disease progression or the last follow-up date. OS was calculated from the date of diagnosis of metastatic disease until the last follow-up or death. Survival analysis was done using Kaplan–Meier estimates and log rank test for bivariate comparisons. The statistical review of the study was performed by a biomedical statistician from our institute.

Results

Our database identified thirty-seven patients of metastatic anorectal melanoma presenting to us between January 2013 and December 2015. Median age at diagnosis was 54 with range from 25 to 87. Table 1 summarizes the patient characteristics.

Treatment characteristics

All the 37 patients included in the study were treated as per the physician's choice in accordance with their age, PS, and comorbidities. Twelve patients did not receive any first-line therapy and were planned for BSC only while the remaining 25 patients received systemic therapy.

The median number of cycles received by patients was 3 with a range from 1 to 12 cycles in the patients who received first-line therapy. Of the 25 patients who received treatment, the best response achieved was a PR in 4 patients (16%), SD in 2 (8%), and PD in 13 (52%) while response data were not available for 6 patients. Of these 6 patients, 4 patients were lost to follow-up, and the remaining 2 patients developed toxicity before response evaluation for which the treatment had to be stopped. Of the 25 patients starting first-line therapy, 15 had PD, treatment was stopped in 4 due to toxicity, 4 were lost to follow-up, and 2 are still on first-line therapy. Eleven patients have been offered second-line therapy.

Progression-free survival

With median follow-up of 56 weeks, the median progression-free survival for patients on first-line therapy was 17 weeks [Figure 1].

Table 1: Baseline demographic and distribution (*n*=37)

Patient characteristics	*n* (%)
Median age (years) (range)	54 (25-87)
Gender	
Male	25 (67.6)
Female	12 (32.4)
Presenting symptoms	
Bleeding per rectum	32 (86.5)
Groin swelling	26 (70.3)
Anorectal pain	18 (48.6)
Altered bowel habits	17 (45.9)
Anal mass	8 (21.6)
Pain (abdomen/back)	7 (18.9)
Paraplegia	2 (5.4)
Primary tumor site	
Anal	15 (40.5)
Rectum	6 (16.2)
Anorectal	16 (43.2)
Prior treatment if any	
Local excision	7 (18.9)
Definitive surgery	4 (10.8)
No treatment	26 (70.3)
Metastatic sites	
Inguinal nodes	26 (70.3)
Pelvic nodes	13 (35.1)
Bone	8 (21.6)
Lung	17 (45.9)
Liver	21 (56.8)
Soft- tissue deposits	4 (10.8)
Peritoneal deposits	2 (5.4)
Adrenal	1 (2.7)
Performance status	
1	16 (43.2)
2	10 (27)
3	9 (24.3)
4	2 (5.4)

Overall survival analysis

The median OS for the whole cohort was 27 weeks [Figure 2]. There was a significant difference in OS in patients who did not receive any first-line therapy as compared to those who received first-line therapy (median OS: 14 vs. 33 weeks; $P = 0.04$) [Figure 3]. When stratified by PS of 0–1 to PS of 2 or more, the patients with PS of 1 did significantly better when compared to PS of 2 more in terms of OS (70 vs. 17 weeks; $P = 0.015$) [Figure 4]. The patients who received second-line therapy at progression had a numerically superior OS, but it was not significant statistically (median OS: 40 vs. 23 weeks; $P = 0.341$).

Discussion

The treatment of choice in anorectal melanoma (ARM) is surgery (abdominoperineal resection vs. wide local excision with or without inguinal node dissection), but outcomes are dismal because of early recurrences with distant metastasis.[20] Median survival, based on metanalysis, ranges from 17 to 21 months with varying outcomes related to surgery performed and extent of disease.

The evidence for systemic therapy in mucosal melanomas, including ARM, is largely extrapolated from cutaneous melanomas, which may not always be a valid comparison. The

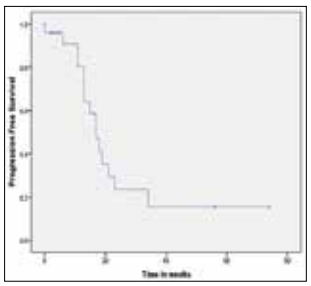

Figure 1: Kaplan–Meir progression-free survival: All patients on first line therapy

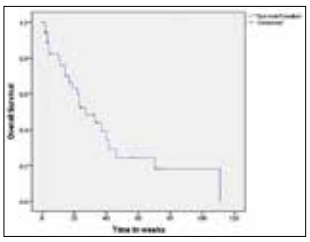

Figure 2: Kaplan–Meir overall survival: All patients

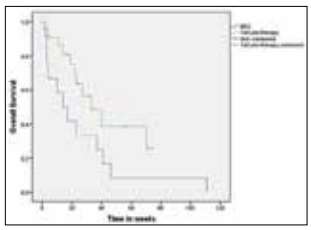

Figure 3: Kaplan–Meir overall survival: First-line therapy versus best supportive care

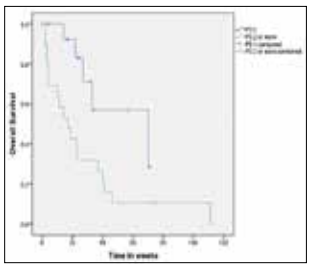

Figure 4: Kaplan–Meir overall survival: Stratified by performance status

relative infrequency of this tumor also means that randomized trials are unlikely and we will have to depend on retrospective data and single-institution studies to form management strategies. Without treatment, the median OS in patients with metastatic disease is around 4 months.[6,21] Median OS for patients receiving palliative treatment is extremely poor and around 6 months as reported by the National Cancer Institute of Milano.[22]

While poor ECOG PS and extensive disease burden often entail patients receiving BSC only, the lack of a standardized treatment protocol also means that a number of fit patients will not receive the benefits of systemic therapy. This is reflected in our study, where 12/37 (32.5%) patients were advised BSC and 25/37 (67.5%) were considered for CT and/or OMCT as per the discretion of treating physician. The median follow-up in our study was of 56 weeks. The OS of patients considered for supportive care was 14 weeks while those received treatment had a median OS of 33 weeks (P = 0.04). This is less than what has been reported in the US where the median survival of patients with anorectal melanomas in the United States is 10 months for those with distant metastasis.[23] Potential reasons for this variance include the disease burden of patients in our study (median number of metastatic sites-2). PS was an important and independent predictor of prognosis in our study on univariate analysis. Patient with a PS of 1 had a significant difference in OS as compared to PS of 2 or more (70 vs. 17 weeks), and this is along expected lines.

The ideal regimen and their response rates in patients with advanced disease remain largely unknown. Many have used biochemotherapy[20-23] (as systemic therapy that included at least one chemotherapeutic agent and at least one biologic agent) to treat advanced metastatic melanoma, mostly in cases of cutaneous origin, and it is associated with the highest response rates among systemic therapy regimens.

This was the basis for use of the in-house OMCT protocol consisting of tamoxifen, propranolol, or thalidomide as an anti angiogenic drug in combination with sodium valproate, metformin, and/or celecoxib. Considering upfront OMCT is not useful as a heavy burden of disease, needs to be down staged with intravenous chemotherapy.

As per the results of our study, we suggest that chemotherapy may be considered in first line as it has shown to have OS benefit in comparison to BSC, especially in patients with good PS of (PS 1). From our study, platinum/paclitaxel or capecitabine/temozolamide regime can be considered as the preferred regime in the resource-limited setting where immunotherapy may not be a feasible option.

The downside of this study and its results are its small number and retrospective nature. These findings need to be justified in a larger cohort and in a prospective randomized manner which seems to be a distant reality owing to smaller number of cases and probably a longer time required to enroll the adequate number of patients for undertaking a study in a randomized fashion. The adverse events and quality of life-related variables for patients on chemotherapy also could not be accurately described.

Conclusion

Metastatic ARM can be offered chemotherapy, especially in good PS patients. Paclitaxel/platinum or capecitabine/temozolomide regime can be considered as the preferred regime in the resource-limited setting where immunotherapy is largely not feasible.

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Conflicts of interest

There are no conflicts of interest.

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